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- (74) Agents: **CORUZZI, Laura, A. et al.**; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).
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- (71) Applicants (*for all designated States except US*): **MEDICAL COLLEGE OF OHIO** [US/US]; 3000 Arlington Avenue, Toledo, OH 43614 (US). **THE UNIVERSITY OF TOLEDO** [US/US]; 2801 West Brancroft Street, Toledo, OH 43606 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **SWIERCZ, Rafal** [US/US]; 1355 Oak Hill Ct., Apt. 69, Toledo, OH 43614 (US). **SELMAN, Steven, H.** [US/US]; 4534 Gran-ville Court, Toledo, OH 43615 (US). **JANKUN, Jerzy** [US/US]; 7014 Oakshade Road, Sylvania, OH 43560 (US). **SKRZYPCZAK-JANKUN, Ewa** [US/US]; 7014 Oakshade Road, Sylvania, OH 43560 (US). **CHOROS-TOWSKA-WYNIMKO, Joanna** [PL/US]; 66A Biel-szowicka Str, PL-04-738, Warsaw (PL).
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(54) Title: MODIFIED PLASMINOGEN ACTIVATOR INHIBITOR TYPE-1 AND METHODS BASED THEREON

(57) Abstract: The present invention is based upon the discovery that modified plasminogen activator inhibitor type-I (PAI-1) in which two or more amino acid residues that do not contain a sulfhydryl group have been replaced with amino acid residues that contain a sulfhydryl group and, therefore, forms intramolecular disulfide bonds, have increased in vivo half-life. Also disclosed are the modified PAI-1 proteins, derivatives and analogs thereof, specific antibodies, nucleic acid molecules and host cells. Methods for producing modified PAI-1, derivatives and analogs are also provided. The invention further relates to Therapeutics, pharmaceutical compositions and method of using the composition for treatment. The invention may be used to inhibit angiogenesis in a subject, thereby treating diseases or conditions associated with undesired angiogenesis and cell proliferation. Such conditions include psoriasis, chronic inflammation, tumor invasion and metastasis and conditions in which angiogenesis is pathogenic. The modified PAI-1 molecules of the present invention are useful for the treatment, prophylaxis, management and amelioration of cardiovascular diseases such as, but not limited to those that are related to hyperfibrinolysis, hemophilia, and vessel leakage syndrome.



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## INTERNATIONAL SEARCH REPORT

International Publication No.  
PCT/US03/06679**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07K 14/00; C07H 1/04; A61K 38/00

US CL : 530/350; 514/2

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350; 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
ISSUED PATENTS\_AA; A\_GENESEQ; PIR\_76

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: MEDLINE, BIOSIS, WPIDS; WEST

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,303,338 B1 (NI ET AL) 16 October 2001 (16/10/01), see the entire document.	1-23
X	WO 97/39028 A1 (AMERICAN NATIONAL RED CROSS) 23 October 1997 (23/10/97), see the entire document.	1-23
X	US 5,639,726 A (LAWRENCE ET AL) 17 June 1997 (17/6/97), see the entire document.	1-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 12 DECEMBER 2003	Date of mailing of the international search report 14 JAN 2004
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Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231  
Facsimile No. (703) 305-3230

Authorized officer

Valerie Bell-Harris for  
HOPE ROBINSON

Telephone No. (703) 308-0196

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.